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(21) International Application Number: PCT/FI98/00412 (22) International Filing Date: 15 May 1998 (15.05.98) (30) Priority Data: <table border="0"><tr><td>60/055,642</td><td>14 August 1997 (14.08.97)</td><td>US</td></tr><tr><td>60/056,409</td><td>25 August 1997 (25.08.97)</td><td>US</td></tr><tr><td>60/056,761</td><td>25 August 1997 (25.08.97)</td><td>US</td></tr><tr><td>60/057,766</td><td>5 September 1997 (05.09.97)</td><td>US</td></tr></table> (71)(72) Applicant and Inventor: GLASS, Joel, Howard [US/FI]; Satakunnankatu 19 D 36, FIN-33210 Tampere (FI). (74) Agent: NIEMINEN, Taisto; Patenttitoimisto T. Nieminen Oy, Kehräsaari B, FIN-33200 Tampere (FI).		60/055,642	14 August 1997 (14.08.97)	US	60/056,409	25 August 1997 (25.08.97)	US	60/056,761	25 August 1997 (25.08.97)	US	60/057,766	5 September 1997 (05.09.97)	US	(81) Designated States: CA, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>With amended claims.</i>
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(54) Title: METHOD FOR EXTRACTING SYNERGISTIC AND BIOLOGICAL ACTIVITY MAINTAINING COMPOUND FROM CAMELLIA SINENSIS; AN EXTRACTED COMPOUND AND USE OF SAID COMPOUND IN THE FOOD PROCESSING OR PHARMACEUTICAL INDUSTRY (57) Abstract <p>A system in which a biologically active compound of catechins, polyphenols and other substances are extracted from Camellia sinensis in an optimally efficient way for industrial production. The raw material is Camellia sinensis and the extraction medium is water. The temperature of the water during the extraction process is a critical factor and should be less than the boiling point of water (the boiling point of water being normally 100 degrees centigrade, depending on altitude) to maintain a biologically active extract. While the extraction medium (water) itself may be heated in a stainless steel (but not aluminium) container (or in non-reactive glass, ceramic, porcelain), the extraction itself process itself where the water and Camellia sinensis leaves are combined, must take place in a non-reactive glass, or ceramic, or porcelain container which is non-metallic.</p>														

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**METHOD FOR EXTRACTING SYNERGISTIC AND BIOLOGICAL
ACTIVITY MAINTAINING COMPOUND FROM CAMELLIA SINENSIS:
AN EXTRACTED COMPOUND AND USE OF SAID COMPOUND IN
THE FOOD PROCESSING OR PHARMACEUTICAL INDUSTRY**

FIELD OF THE INVENTION:

The invention relates to an extraction process which results in the production of a biologically active extract compound of catechins, polyphenols and other substances derived from *Camellia sinensis* in a process suitable for industrial production of processed foods and pharmaceutical prescription and non-prescription medications using the *Camellia sinensis* extract which may be utilized in the form of a powder, or a liquid, or a semi-liquid form.

BACKGROUND OF THE INVENTION:

Extraction process of solid ingredients from plants may be achieved in a number of ways. These include alcohol extracts, extracts through the use of various chemicals, extracting through water as an extract medium at various possible temperatures which normally includes boiling the raw materials in water, or physical pressure applied to the raw materials.

In the case of *Camellia sinensis* several methods involving chemicals, alcohol, and water will produce an extract. However the objective of the present invention is to produce an extract which maintains specific biological activities, and which will contain catechins/polyphenols as well as other ingredients found in the raw material *Camellia sinensis*. Use of solvents other than water produce variations in the composition of the extract which are unwanted, and which furthermore degrade the quality of the catechins/polyphenols and other ingredients. Furthermore, some of the solvents often remain in the extract, and this is not desirable.

It is an objective of the present invention to produce a biologically active extract which contains catechins, polyphenols and other substances, all maintaining biological activity. Therefore alcohol-medium extraction and chemical-medium extraction is not utilized in the present invention. The present invention utilizes water as a medium of extraction.

It is an objective of the present invention to produce biologically active extract from *Camellia sinensis* by control of the temperature of the water during the extraction process. To secure the optimal extraction of a synergistically effective *Camellia sinensis* extract, and to assure the optimal extraction process, the water must remain at a temperature below the boiling point of water. The temperature of the water at the beginning of the extraction process should range

approximately between 60 degrees C up to approximately 99 degrees C, but not as high as the temperature at which water boils, meaning not as high as 100 degrees C. The optimal temperature range of the present invention would be approximately between 80 degrees C and the boiling point of water. The process involves beginning contact between the raw material, *Camellia sinensis* at or close to the highest temperature which the water will be during the entire process, and allowing the extraction process to occur while the water either remains at that temperature or is cooling from its highest temperature.

It is an objective of the present invention to begin the process with a water temperature at a heat level which accomplishes two things: one it extracts the relevant catechins, polyphenols and other substances which are desired for the synergistic compound to be extracted; and two it does not destroy the biological activities of the extracted substances. Therefore the water must never reach the boiling point (100 degrees C). Boiling the raw material will cause two problems: one, it can destroy the biological activity of the extract; and two, it will extract substances additional to the catechins, polyphenols and other desired substances in amounts and qualities which are unsuitable for the end use of food additives or medications. These additional substances and improper balance of the extract, caused by boiling the *Camellia sinensis* in an extraction medium will act against the effectiveness of the extract.

It is an objective of the present invention to have the maximum temperature of the extraction medium (water) less than the boiling point of water, and for example beginning within the approximate range of 60 - 99 degrees as a starting point (but this may be higher or lower as long as the boiling point of water is not reached) and then to achieve certain objectives as to the percentage of catechins/polyphenols in the extract either to lower that water temperature by maintaining the initial temperature or through absence of applied heat to the production process and through exposure to the solution and processing equipment to normal room temperature, or to increase or maintain the heat of the water during the extraction process.

It is an objective of the present invention to have the extraction process take place in a container which is non-reactive with the liquid extract. This container must be glass, ceramic, porcelain or other non-reactive form of container. Metal containers (particularly aluminium) are not suitable for the extraction process. The water itself may be heated in a stainless steel container (preferably not aluminium), or in a glass, or ceramic, or porcelain container. But the extraction itself must take place in a non-reactive, non-metallic container.

It is the object of the present invention to produce the maximum amount of the extract solids from the raw materials based on a process which will produce a biologically active extract with approximately 50% polyphenols for example for use in the food processing industry. The extraction process itself may be based on a single extraction activity or a triple (or more) extraction activity.

The multiple extraction activity meaning that up to three times water is may be added to the raw materials, and after one of the three extractions the water is drawn off. The extraction process may take place less than three times with the same raw materials. The extraction process may also take place more than three times with the same raw material, but after the third extraction, the nature of the solids is degraded, and furthermore the composition of the compound starts to vary from the desired compound to be used in food processing or for the pharmaceutical industry. During, for example, a fourth or fifth extraction period using the same raw materials, the raw materials are subjected an extraction process in which problems may occur which include the following: extraction is inefficient, and extraction produces an extract which is out of balance in its composition with the extraction of the first three extractions of the raw materials (less of desired materials and the introduction of undesirable materials take place during the fourth extraction procedure of the same raw materials).

The single extraction activity meaning that the *Camellia sinensis* raw material is exposed to the water extractant just one time. This being for approximately 20 - 40 minutes. For industrial production, the single extraction activity is preferred because it produces a more standardized extract and does so more quickly than the multiple extraction activity.

It is also the objective of the present invention to produce the maximum amount of the desired composition extract which is biologically active and which is approximately 50% polyphenols, and this is accomplished through controlling the ratio of raw materials to extraction medium, and the temperature and length of time of the extraction process in which the *Camellia sinensis* raw material is in contact with the extraction medium, water. Regarding the ratio of polyphenols in the extract solids, while the present invention is not limited to the following ratios, the present invention targets the extraction process to produce extract with pre-designed levels of catechins/polyphenols. The percentage level of catechins/polyphenols which is the objective of the extraction process is determined by the use for which the extract will be put to use. For example, for pharmaceutical purposes related to acute high blood pressure and cardio-vascular disease, the catechin/polyphenol extraction level would be at approximately 80% - 95% of the extract. For example, for use in the food processing industry, the level could be 50 % catechins/

polyphenols. Of the polyphenol content, approximately 50% will be EGCG. This conforms to a natural, synergistic balance of *Camellia sinensis* itself, and differs from highly concentrated EGCG extracts, which are in effect a chemicalized powerful antioxidant, which should be provided only under medical supervision and in limited amounts over a short period of time. The above concentrations of polyphenols as per centages of the total extract solids does not limit the scope and rights of the invention but is for illustrative purposes only. It is possible, depending on the specific use instance of a food to be preserved or whether the food is intended to lower serum cholesterol levels, that 90% catechin/ polyphenol level could be used or 50% polyphenol/catechin level could be used. The point is that the extraction process targets a particular use of the extract and produces the relevant level of catechin/polyphenol per centage of the total extract.

By determining the time the extraction medium (water) is in contact with the *Camellia sinensis*, and by determining the temperature of the water, the amount of catechins/polyphenol in the extract can be controlled. As mentioned for illustration purposes, object production levels of catechin/ polyphenol extraction for use in the food processing and medical industry would be approximately 20 - 45% polyphenols, 40 - 50% -65% polyphenols, or 80 - 95% polyphenols. these percentages may be varied and are set by the use of the extract. But the process will produce any desired per centage of catechins/polyphenols, and the rights of the present invention are not limited to the above figures.

The present invention may use a wide range of *Camellia sinensis* per liter of water, but for the purpose of illustration and general industrial production it is possible to utilize approximately 50g of *Camellia sinensis* per liter of water. For example in an industrial batch production of the extract, 100 liters of water would be combined with 5 kilos of *Camellia sinensis*, this however is just an example and does not restrict the rights of the patent, and there is a wide range of possible combination levels of extraction medium to the raw material.

Said combination of 50gm *Camellia sinensis* per liter of water, will produce a 2% solid liquid extract, which results in a dry weight of 20gm *Camellia sinensis* extract per liter of water.

It is also the objective of the present invention to produce an extract which is synergistic, in terms of its positive effect on human health. Thus, the 50% of the extract which is not polyphenols, contains natural tea constituents, such as copper, which acts to increase the efficacy of the polyphenols as an antioxidant, as an anticarcinogen, as an antibacterial agent, and as an anticholesterol agent.

This differs from other *Camellia sinensis* extracts, which are almost 100% polyphenols, and in particular mostly the EGCG variety of polyphenol. These almost totally polyphenol extracts, lack tea constituents which would render the extract a synergistic substance. Thus in the extract of the present invention process, the 25% EGCG of the extract may have more activity (due to synergistic components of the extract) than the 50% or more EGCG of other extraction processes.

It is also the objective of the present invention to have the extraction process occur in a time frame suitable to production of both maximal output and production of biologically active extract. The time is related to the temperature of the extraction media, water. Generally, the minimum time for the extraction process, even at the highest possible temperature (which would be initially just below the boiling point of water and then dropping as the solution is and extraction equipment is exposed to room temperature) is two minutes. But for industrial productions it may remain 20 to 40 minutes or longer provided the water is maintained at a constant temperature between 80 - 99 degrees C.

While the single 20 - 40 minute extraction activity at between 80 - 99 degrees is appropriate to produced the desired balanced extract of 50% polyphenols and 50% *Camellia sinensis* ingredients which act synergistically together.

It is also the objective of the present invention to provide the extract in a form which is easily transportable and which has a long storage life. Therefore, the extract may be further processed into a powder. This may include use of spray dryers, spray bed driers, falling film evaporators, spin flash driers, fluid bed systems and so on. The extract may also be freeze dried. As an alternative to spray drying and other types of food processing drying, it would be possible to utilize microencapsulation or microsphere absorption of the liquid *Camellia sinensis* extract.

It is an objective of the present invention to provide a biologically active extract which may be used by the food processing industry and/or the pharmaceutical industry. The extract of the present invention may be used as the original liquid extract, it may be used as the powder or crystal form itself derived from the liquid extract; or it may be utilized as a liquid made from the extract powder. In the case converting the powder to a liquid at various concentrations, it is important never to boil the new extract liquid and it is best if the temperature of the new extract liquid from powder remain less than the boiling point of water, although there is a wide range of temperatures which may be used by this process with the exception of not reaching 100 dgrs C.

PHARMACEUTICAL USE OF THE INVENTED COMPOUND

The present invention achieves a lowering and balance of serum cholesterol level in one part through its activity on the liver. Thus the *Camellia sinensis* extract will lower both serum and liver cholesterol level. Whereas some approaches to cholesterol control concentrate on reducing absorption (usually in the intestines), examples being phytosterols such as sitosterol and sitostanol; and whereas some approaches (normally medication under the care of a physician) attempt to reduce synthesis of cholesterol in the body; the present invention accomplishes both functions and produces a balanced self-stabilizing cholesterol cycle in the body within the normal healthful cholesterol profile range.

The second means through which the present invention lowers high level serum LDL cholesterol levels, is through absorption. Thus the present invention has the double mechanism of both absorption and synthesis reduction.

The basis of the extract is *Camellia sinensis*. Numerous studies verify that *Camellia sinensis* or some of its constituents, when part of the diet, lowers high serum cholesterol levels. There are a wide range of these studies, and the following are given as example only: K. Muramatsu and Y. Hara, *J. Nutr. Sci Vitaminol*, 32, 613 (1986); K. Goto, S. Kanaya, and Y. Hara, *Proc. of the International Symp. on Tea Science*, 314 (Shizuoka, Japan, August 1991); K. Muramatsu; M. Fukuyo, and Y. Hara, "Effect of Green Tea Catechins on Plasma Cholesterol Level in Cholesterol-fed Rats", Laboratory of Food and Nutrition, Department of Agricultural Chemistry, Shizuoka University, Japan; I. Ikeda, Y. Imasato, E. Sasaki, M. Nakayama, H. Nagao, T. F. Yayabe, and M. Sugano, "Tea catechins decrease micellar solubility and intestinal absorption of cholesterol in rats", Laboratory of Nutrition Chemistry, Kyushu University; S. Kono, N. Ikeada, F. Yanai, and K. Imanishi, "Green Tea Consumption and Serum Lipid Profiles: A Cross-Sectional Study in Northern Kyushu, Japan", Department of Public Health, National Defense Medical College, Fukuoka, Japan.

The present invention deals with the type of tea leaf, and the desired formulation of the extract from the *Camellia sinensis* leaves which will lower both absorption and synthesis of excess serum LDL cholesterol levels.

Commercial teas are generally unsuitable for the raw material, because they have been processed in some way. The leaf must be dried naturally and undergo minimum processing to secure optimal extraction results. Given the variations in processing green leaves of *Camellia*

sinensis, there are variations in catechin/polyphenol content. The level of these critical elements also depends on the age of the leaf and the part of the plant from which it is taken. The present invention can utilize a wide range of *Camellia sinensis* leaves, regarding both age, location on the plant, and the type of processing given the tea leaves. Optimal results, do occur, however, when the leaves are relatively unprocessed and initially contain the highest level of catechins/polyphenols.

The main substance as both an active ingredient, and also as the component in which other components of the extract act with in synergism, in which the present invention is catechins/polyphenols, also classed as tannins. Catechins/Polyphenols are water soluble compounds which have a high potential to oxidize. This makes catechins/polyphenols one of the most potent antioxidants, and they are in fact superior to the vitamin group of antioxidants.

The percentage formulation of the extract depends on the objectives, those objectives being based on the cholesterol profile status of the individual taking the *Camellia sinensis* extract. For example, according to the present invention, individuals who would be identified by a physician as having a very high cholesterol level (for example TC (mg/dl) 277.7+ - 70, and TG (mg/dl) 158+ - 17.6) and perhaps other signs of cardio-vascular disease, would be targeted for a formulation very high in per centage of catechins/polyphenols, for example 90% catechin/polyphenol content, relative to the rest of the extracted components from the *Camellia sinensis* leaves. While an individual which has only moderately elevated cholesterol levels would be targeted for a n extract formulation containing approximately 25% - 45% catechin/polyphenol content. To those familiar with patent applications it will be clear that the present invention is not limited to the above mentioned per centages of catechins/polyphenols in the formulation, but that these are indicative of potimal formulations and that a wider range of formulations is also covered by the present patent application.

To give by way of illustration, a more complete breakdown of a formulation targeted for those individuals with either moderate excess in serum cholesterol level follows: (Note that the per centage amount components can be configured to be in excess of 100% in this illustration if one utilizes the maximal per centages for each ingredient. But this would of course be avoided in the actual formulation of the extract itself. In the extraction process and the variation in leaf content, there is always resome minor variation of the targeted extract itself, but these minor differences are not significant in terms of the overall formulation being effective within the organism. The amounts given here are desirable amounts for the lowering of serum cholesterol level within a range of which these figures are the maximum for optimal performance as a food

ingredient). An effective formulation of *Camellia sinensis* extract, which is the present invention, for the purpose of lowering serum cholesterol levels as an ingredient for the food processing industry has the catechins/polyphenol level at about 25% -50% of the extract. Other components of the extract formulation would be as follows: Flavonols and other flavanoids 14%. Theogallin and other depsides 3%, Organic acids 7%, minerals 8%, amino acids 12%, Carbohydrates 15%, Methylxanthines 8%, less than 1% volatiles, ascorbic acid 1%.

The key components within the catechin/polyphenol category will be the epigallocatechin and epigallocatechin gallate, although there can be up to 16 or more catechins/polyphenols present. If said Catechins are ingested in isolation, they will produce what is a therapeutic medical effect, and according to the present invention could be utilized only for a limited amount of time, meaning from one to several months depending on the particular case of extremely elevated serum cholesterol levels. For example, the present invention utilizes approximately 400 mg/day to 1,000mg/day of 90% catechin/polyphenol extract to achieve a medically therapeutic quickly acting result for extremely high serum cholesterol levels. After one or more months, the serum cholesterol profile will be substantially reduced, and the second formulation of the present invention, containing a lower percentage of catechins/polyphenols could be utilized. The rights of the present invention are not limited to the above figures, but these are illustrative of the general range in which the invention is highly effective. The invention will be effective with wide variance of dosage, and this too is covered by patent rights.

The present invention, for individuals who have elevated but not extraordinarily high serum cholesterol levels, would utilize the formulation of 40 - 60% catechin/polyphenol *Camellia sinensis* extract at a level of approximately between 400mg to 1,500 mg/day or more, about half of which is polyphenols, of which half the polyphenols is composed of EGCG. But again it must be stated that the present invention is not limited by these figures. For example, according to the present invention, a level of approximately 40% - 60% catechin/polyphenol *Camellia sinensis* extract, is effective in lowering cholesterol levels when utilized either as a medication taken in isolation or as an ingredient in processed foods. This too is covered by patent rights on the present invention, for example.

The effect on serum and liver cholesterol profile is in either case (very high serum cholesterol levels, and less elevated but higher than normal serum cholesterol levels, based on lowering LDL cholesterol. Utilizing the present invention, the beneficial cholesterol, HDL cholesterol grow either in terms of their relation to LDL cholesterol, or absolutely. In no case are the HDL cholesterol decreased.

Biliary cholesterol is a major means of sterol elimination from the human body. Biliary cholesterol is itself formed from free cholesterol in the body which is of two types (pre-existing, and as it is newly synthesized). In particular, newly synthesized cholesterol Sunthase. The present invention in part accomplishes the function of lowering LDL cholesterol levels, through its effect on bile and on the liver. Cholesterol is transported into bile. The present invention prevents accumulation of cholesterol in the liver, and promotes the activity of Fatty Acid.

BRIEF DESCRIPTION OF DRAWING

Fig. 1 presents one embodiment of package 4 of food consisting invented extract. The package consists of three layers of food material. The lowest layer 3 is liquid *Camellia sinensis* extract. The next layer 2 is made of jelly and the top layer 1 is made of yogurt. It is very important for the extract to be placed under jelly thus being non-contact with yogurt layer. The extract will then maintain it's activity a long time. Before eating the materials will be mixed. This is one example of food consisting invented extract.

USE AGAINST DENTAL CARIES

The present invention is based on the use of the plant *Camellia sinensis*. The particular substance which inhibits dental caries is an extract of *Camellia sinensis*. This substance achieves highly effective reduction or elimination of dental caries through the action of the *Camellia sinensis* extract to reduce or inhibit the microbe *Streptococcus mutans*. Thus it is primarily the anti-micro-bal effect of the *Camellia sinensis* extract which leads to effectiveness in reducing or eliminating dental caries.

Streptococcus mutans are the precursors to dental caries in that their activity produces acid with destroys tooth substances, causing holes or caries. If the *Streptococcus mutans* is inhibited, then acid will not be formed and caries will not be formed. The present invention accomplishes the function of inhibiting *Streptococcus mutans* in a non-toxic way, and in a way not injurious to human health (as would repeated use of antibiotics, which would also inhibit *Streptococcus mutans*). Through daily application of the extract to tooth surfaces and the mouth, in many types of forms (such as commercial dental products, such as toothpastes or mouthwashes), or for example additionally in the form of professional dental topical applications, the *Camellis sinensis* extract will reduce or eliminate dental caries through its activity to inhibit *Streptococcus mutans*.

It has been noted that dental caries are lower in areas where green tea is part of the diet. Green tea is made from *Camellia sinensis*. Furthermore, green tea has been provided as part of the

diet in animal studies and has been seen to lower dental carie level in hamsters (Hao Yu, Takahiko Oho, Shoko Tagomori, and Toshio Morioka, "Anticariogenic Effects of Green Tea", Department of Preventive Dentistry, Kyushu University, Japan, 1992), however, the mechanism for the effect was unknown. the present invention recognizes the effect as resulting from the powerful antimicrobial activity of green tea. The present invention utilizes the antimicrobial activity of *Camellia sinensis* to inhibit the *Streptococcus mutans*, the bacteria which causes the formation of acid and dental caries. This anticariogenic effect can be maintained or even improved through use of an extract of *Camellia sinensis*, as opposed to having green tea as part of the diet. An extract of *Camellia sinensis*, provides for the antimicrobial activity of *Camellia sinensis* to be made available for specifically dental applications, both in consumer products and in professional topical applications.

The inventor of the present invention has provisional patent status (PPA number 60/056,761) on the extraction process itself. The extraction process provides for extraction through use of non-toxic extraction medium, thus providing a chemically uncontaminated extract suitable for oral use on a regular basis without side effects.

The anticariogenic activity of *Camellia sinensis* extract is based primarily on the ability of tea catechins to inhibit the activity of multiple forms of *Streptococcus mutans*. Said tea catechins are found in concentration in the extract of *Camellia sinensis*. The extract of the present invention, further contains 50% *Camellia sinensis* contents which are not Catechins/polyphenols, but which act to produce a synergistic effect in inhibiting *Streptococcus mutans*. Copper is one example of this synergistic action production constituent, which is found naturally in *Camellia sinensis* and in the extract of the present invention.

The Minimum Inhibitory Concentration of the *Camellia sinensis* extract in dental products to inhibit *Streptococcus mutans* depends on the nature of the other constituents of the dental preparation, but would generally start as 1/50 and go to 1/2,500 or more.

Camellia sinensis extract has further beneficial effect on oral health, which are covered by the present invention patent: these include an ability to remove plaque from teeth, and through the antienzymatic activity of the extract to inhibit collagenolytic effect of *Porphyromonas gingivalis*.

The antiplaque activity of the *Camellia sinensis* extract results from a combination of chemical and ionic activities. Regarding the ionic activities, to achieve the most effective result of the *Camellia sinensis* extract as a plaque remover, the extract must be heated above room

temperature, thus increasing the ionic activity of the extract. While a wide temperature range is possible for the anti-plaque activity, and is covered by the present patent application, approximately from 40 - 80 degrees C provides an optimal anti-plaque activity. Clearly these high temperatures relate to professional dental treatment for plaque removal more than home care, but even at room temperature, the *Camellia sinensis* extract will have a therapeutic effect in plaque removal. Therefore, as an antiplaque agent, perhaps the *Camellia sinensis* extract is best utilized as a professional topical application by dentists, rather than as a consumer product.

Concentration of the 50% polyphenol extract for the purpose of targeted therapeutic plaque removal would be approximately 1/50, but rights to the present invention are not limited to this concentration, which is given as example.

USE AS A FOOD PRESERVATIVE ANTIOXIDANT AND ANTIMICROBAL

Present type perservatives used by the food processing industry as antibacterial or antioxidant normally have negative impact on health in large amounts (the exception being ascorbic acid). Examples would be nitrates / nitrides, BHA / BHT (used in foods with high fat and oil content to prevent or slow oxidation which results in flavor and color and quality changes), Sulfites, and others.

Nitrates and Nitrides are used primarily in meats to inhibit the growth of the deadly bacteria *Clostridium botulinum*. Unfortunately Nitrates and Nitrides combine with amines both in foods themselves and inside the human body, producing carcinogenic substances, nitrosamines, which are highly potent carcinogeni substances. Nitrades and Nitrides also combine with heomglobin, producing blood abnormalities. And Nitrates and Nitrides act against a range of beneficial bacteria including those necessary to human health and normally found in the stomach and intestines such as *Asidofilus* or *Bifidus*. Yet because Nitrates and Nitrides act against the formulation of tobulinum toxin (for example in smoked fish), its use is required by most national food regulatory agencies such as the FDA in the United States of America. In the case of smoked fish, sodium nitrite must be present in 100 to 200 parts per million according to the FDA.

So clearly an alternative food preservative for meats and other foods which has less of a negative impact on human health needs to be found.

The present invention, which is a combination of polyphenols and other ingredients in specific amounts, derived as an extract from *Camellia sinensis*, fulfills that objective. The present

invention inhibits the growth of *Clostridium botulinum* bacteria (thus having use in the meat food processing industry) but does not combine with amines either in food or in the body.

Furthermore, the present invention does not combine with hemoglobin. And the present invention does not effect beneficial bacteria such as *Asidofilus* or *Bifidus*. Thus the present invention may act as a replacement for Nitrates and Nitrides.

Recent studies suggest that high levels of BHA and BHT can cause cancer in the stomachs of rats, mice and hamsters, and liver cancers in fish. BHA and BHT have toxic properties and are limited to 0.02 per cent or 200 parts per million of the oil or fat content of the food ind which it is used. The present invention (specified combination of polyphenols and other ingredients derived in extraction process from *Camellia sinensis*) may also act as replacement for BHA and BHT. The present invention acts as a super antioxidant, haveing approximately 20 times the antioxidizing power of Vitamin E, for example.

Sulfites are used mostly as antioxidants to inhibit bacterial growth in alcoholic beverages, such as in wine. Sulfites are also used to prevent color changes in solid foods such as processed fruits and vegetables. Common names of sulfites include, sulfur dioxide, sodium sulfite, sodium and potassium bisulfite, and sodium and poptassium metabisulfite. Negative effects of sulfites include their destruction of thiamin in the foods in which they are placed and in the human body. Also, certain types of individuals (for example, asthmatics or otherwise highly allergic individuals) may have an allergic reaction to sulfites. The present invention is a nonharmful replacement for sulfites due to the high level antioxidant effect of the present invention.

The present invention provides forms of *Camellia sinensis* extract which perform the food preservation functions of Nitrates / Nitrides, BHA / BHT, and sulfites, without any of the harmful side effects of those commonly used preservatives. Thus the present invention can play an important role in the food processing industry by providing a food preservative which is non-toxic and nonharmful but which performs the required functions of presently utilized food preservatives which are toxic and in some cases carcinogenic.

The present invention is comprised of a several forms of extract of *Camellia sinensis*. The exact composition of the extract is determined by the function the extract will play as a food preservative. The following examples are for illustration and do not limite the rights of the present invention to those forumlations presented here. For example, if the function is more antioxidant (as a replacement for BHA and BHT for example), then the level of catechins/ polyphenols will be high in the extract, above 30% and may reach 90% or more. If, for example

the function is antimicrobial (as a replacement for Nitrates and Nitrides), then the catechin/polyphenol is well complimented by other components of the extract and may be in the lower range of the 90% to 30% possible concentration of polyphenols. And if the function of the food preservative is both antimicrobial and antioxidant, as it is in most cases, then it is possible to use several extract combinations together (for example combining extract form A. with 30% - 50% polyphenols, with extract type B containing 50 - 60% catechins/polyphenols, with extract type C containing around 90% catechins/polyphenols).

When used as an antioxidant for food preservative, the catechin/polyphenol (flavanol) content of the *Camellia sinensis* extract may be in the upper range of the 30% to 90% content. This is because the active antioxidant is the tea *Camellia sinensis* catechin/polyphenol.

Regarding the concentration of the total antioxidant *Camellia sinensis* extract (when utilized as an antioxidant) in foods, it depends on the fat content and composition of the food. Because processed foods are complex and have various constituents, which require antioxidant protection at different rates and concentrations, the strategy of combining various forms of the extract (relative to catechin/polyphenol content) could be utilized. The concentration of the extracts themselves is done in mg/kilo and takes into account the following factors: fat content, type of fat or oil, how the fat or oil has been processed, and other ingredients in the food which may require antioxidation protection (such as meat, vegetables and so on). Generally speaking we can say that antioxidant activity of the *Camellia sinensis* extract follows a bell-shaped curve, meaning that up to a point of mg/kilo concentration it becomes more effective as an antioxidant, and then after a certain concentration point of mg/kilo it becomes less effective. This loss of effectiveness with increasing concentration of mg (of the *Camellia sinensis* extract) per kilo (of processed food product) increases to the point where an implosion occurs, an oxidizing reaction from excess *Camellia sinensis* antioxidant extract. Basically this principle must be applied to each particular food, and each food will have its own profile both for minimal, optimal, and excess mg / kilo. By means of example, we may say that cereal products with oil or fat content (such as cookies) would be in the range of 10 mg/kilo - 1 g/kilo. Although the concentration profile of extract to food product depends on the polyphenol concentration of the extract itself, and the oil/fat and other composition of the food itself.

The other components of the *Camellia sinensis* tea extract which can play a positive role in antimicrobial activity (and also by-the-way antioxidant activity) in addition to the catechins/polyphenols include but are not limited to alkaloids, volatile flavor compounds, theaflavins, thearubigins, non-phenolic pigments, amino acids, metals, vitamins, and so on.

Regarding the concentration of the *Camellia sinensis* extract (when utilized as an antimicrobial substance) the concentration of the extract utilized in a particular food depends on the type of food. For example the mg (of *Camellia sinensis* extract) per kilo of processed food product would be different for processed meats than for used in smoked fish or in processed vegetables. Furthermore the concentration of the *Camellia sinensis* extract per kilo of processed foods, depends also on the composition of the extract itself, meaning the per centage of catechins/polyphenols. Generally speaking, the antimicrobial activity may focus in the mid-range of catechin/polyphenol concentration (between 40% to 90% polyphenols), because there are other factors in the extract which act as an antimicrobial in addition to the catechins/polyphenols, and which would be of use for this function as a food preservative. The exact amount, again depends on the type of processed food being preserved.

The present invention utilizes as Minimum Inhibitory Concentration (MIC) of *Camellia sinensis* extract of 50% polyphenols against the most virulent pathogens, such as *Clostridium botulinum* relative to the meat processing industry, an MIC of the *Camellia sinensis* extract diluted to a factor of 1/50 or 1/500 or perhaps even 1/2,500 depending upon the food and its other contents in which the *Camellia sinensis* extract was included.

For products such as meats, the approach could be to utilize one form of the *Camellia sinensis* extract, or combining several concentrations of polyphenol *Camellia sinensis* extracts (for example a 25% - 40% catechin/polyphenol extract, combined with a 40% - 50% catechin/polyphenol extract, combined with an 80% - 90% catechin/polyphenol extract). Again there is a profile for the *Camellia sinensis* extract, meaning minimal amount, optimal amount, and maximum amount; these determined specifically for each food type and composition to be preserved through antimicrobial action. Further, the food processing activity itself has to be considered, when formulating the optimal formulation and concentration of the *Camellia sinensis* extract as antimicrobial (for example, is the food heated or frozen after adding the *Camellia sinensis* extract, and at what temperatures and how long. Packaging may also be considered in developing the optimal profile for the *Camellia sinensis* extract.

The best strategy for *Camellia sinensis* extract for antimicrobial action is either as an optimal concentration of mg (of extract) per kilo (of processed food) based on one form of the extract (meaning a particular per centage of catechins/polyphenols in the extract); or by combining two or more forms of the extract (meaning particular per centage of polyphenols in each form of the extract), in particular amounts in the processed food.

For example in processed meat such as hot dogs or sausages, the fat content and type of meat plays an important role in determining the polyphenol content of the extract or extracts of *Camellia sinensis* as well of determining the amount of extract (or extracts) per kilo of meat product.

When determining the optimal level of *Camellia sinensis* extract for use in food products for the purpose of antimicrobial action, the activity of the *Camellia sinensis* extract as an antioxidant, which may form an oxidizing reaction when utilized in too high amounts, should be considered. Therefore a balance between antimicrobial and excess antioxidantizing activity must be attained. For this reason in meats, the lower range of catechin/polyphenol content (between 90% and 30% polyphenols) is utilized in the preservation of meats. However this depends on the type of meat and on the fat content, and the upper range may be utilized as well.

Generally, as an antimicrobial for meats, to replace or reduce Nitrates and Nitrides, the use of a 90% polyphenol *Camellia sinensis* extract would result in a concentration in the meat product between approximately between 0.08 gm/kilo and 10gm/kilo more or less; while the standard synergistic extract of the present invention, at a level of 50% polyphenols, would have a MIC of approximately 1.6 gm/kilo and 20gm/kilo more or less, although the scope present invention is not limited to this formulation, which is presented for the purpose of example. There could be for the case of preserving such meats through the inhibition of *Clostridium botulinum* also a combination of 35%, 45%, 90% catechin/polyphenol *Camellia sinensis* extract, also within the range of 0.04 gm/kilo and 20gm/kilo more or less, the exact amount of total extract per kilo varying from that of the single concentration (of catechin/polyphenol) extract.

CAMELLIA SINENSIS EXTRACT, CHEMOPREVENTATIVE EFFECT TARGETED TO REDUCE MARKER LEVEL ASSOCIATED WITH LUNG CANCER AMONG CIGARETTE SMOKERS

Camellia sinensis has been found in epidemiological studies, computer studies, and laboratory studies involving animals and human beings to have significant anticarcinogenic effects. It acts against the formation of several types of cancer both on the formative stage of cancer and in the promotional stage when the cancer normally grows and spreads.

It is the objective of the present invention to utilize *Camellia sinensis* polyphenols, and in particular epigallocatechin gallate (EGCG) in a stable, biologically active powder form, which characterizes the makeup of unstable liquid *Camellia sinensis* extract in its contents and in the

relative composition of the various contents. Specifically that EGCG is not in isolation or concentration, but is about 25% of the extract powder, and total polyphenols about half the extract powder.

It is also the objective of the present invention that the powder extract have in the remaining 50% non-polyphenol constituents, the makeup which acts to synergize the active polyphenol ingredients as an anticarcinogen.

It is also the objective of the present invention that the remaining 50% non-polyphenol constituents act as a biological break against unwanted oxidation reactions from EGCG concentrations.

And it is the objective of the present invention that said *Camellia sinensis* powder retain biological activity as an anticarcinogen throughout use in the food processing industry, so that it may serve as a nutraceutical, a non pharmaceutical food substances which possesses activities conducive to good human health.

It is further the objective of the present invention that said formulation will have an effects of urokinase enzyme inhibition and super-antioxidation as a means to lower serum SCE marker levels for cigarette smokers to normal range SCE levels of non-smokers.

ENZYME INHIBITION AS AN ANTI-CARCINOGEN

Studies in 1997 at the Medical College of Ohio, USA, by Dr. Jerzy Janku, Ewa, University of Toledo, Ohio and a research group, has shown that one of the tea polyphenols has the effect of preventing and reducing the spread of cancer. (Why Drinking Tea Could Prevent Cancer, Nature 387, p.561). The anti-carcinogenic activity is derived in part from the active ingredient epigallocatechin gallate(EGCG), which interferes with development and existence of and functioning of urokinase, which is an enzyme found in the human body necessary for the growth of cancerous cells.

The study was done by computer-based molecular research, which determined which compound in *Camellia sinensis* would block the activity of urokinase.

The medical blocking ingredient for urokinase, is a pharmaceutical (Amiloride); and Amiloride is in fact more effective in blocking urokinase. However, Amiloride is itself toxic and can produce

unwanted side effects. Therefore consumption of Amiloride must be limited to 20mg per day.

EGCG may be consumed in liquid tea 600mg EGCG as part of the entire tea complex or far more per day with no toxicity or side effects.

ANTIOXIDANT ACTIVITY AS AN ANTI-CARCINOGEN

Another reason which *Camellia sinensis* has anti-carcinogenic action is its activity as a super-antioxidant. At the annual meeting of the American Chemical Society on September 11, 1997; research at the University of Kansas was announced which determined that EGCG was shown to be 100 times more effective than Vitamin C and 25 times more effective than Vitamin E in destroying free radicals (free radicals causing cellular damage including causing breaks in DNA).

It is the objective of the present invention to provide EGCG not in isolation, but along with the constituents normally found in the leaf of *Camellia sinensis*. The present invention is based on the assumption that to provide EGCG in isolation is to provide a highly refined chemical that may be harmful to health, and which may produce unwanted results. For example, the present invention theorizes that EGCG in isolated concentration may produce the opposite result of antioxidation, and may cause an unwanted oxidation reaction. When iron found in the human body may combine with isolated EGCG, then the already unwanted oxidation reaction is synergized, thus producing a super detrimental oxidation reaction which is extremely powerful and has consequently powerful negative effects the opposite of what are desired from EGCG.

Therefore the present invention has the objective of providing EGCG in the natural amount found in *Camellia sinensis*, along with the non-polyphenol ingredients of green tea which promote positive activity, while putting biological breaks on unwanted activities such as oxidation.

EPIDEMIOLOGICAL STUDIES

That *Camellia sinensis* has anticarcinogenic activities is also demonstrated in epidemiological studies. For example in "The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China", *Cancer* 1996 June 15; 77(12):2449-57, it was found that green tea consumption demonstrates an inverse association with cancers of this type. For example in the study by the US National Cancer Institute (NCI) and the Shanghai Cancer Institute, it was found in 1990 that there is an

inverse association of Esophageal Cancer with drinking green tea. And for example, I. Oguni et al, Japanese Journal of Nutrition, 47, 31 (1989) demonstrated a significantly lower death rate for all types of cancers among population who drank green tea.

CELLULAR AND ANIMAL LABORATORY STUDIES

There are numerous studies which show a clear anticarcinogenic effect of *Camellia sinensis*. These include: I. Oguni et al. Biol. Chem, 52, 1879 (1988); the study that *Camellia sinensis* and its Catechins inhibit initiation and promotion of cancer in cells by Y. Nakamura et al, PROC. of International Tea-Quality Human Health Symposium, pp. 227-238 (Hangzhou, China November 1987). Fujiki Suganuma et al, "Sarcophytol A and (-)-epigallocatechin gallate (EGCG), non-toxic inhibitors of cancer development", in Cancer Chemoprevention, CRC Press, London, pp. 393-405, 1992; and among many more one particularly relevant to the present invention as the *Camellia sinensis* extract as a protection against cancer related to cigarette smoking: Taniguchi S. et al, "Effect of (-)-epigallocatechin gallate, the main constituent of green tea, on lung metastasis with mouse B16 melanoma cell lines", Cancer Lett, 65: 51-54, 1992.

HUMAN STUDIES

Chemopreventive effects of green tea and coffee among cigarette smokers were examined among 52 male subjects. Results linked to the study of SCE markers for development of cancer indicated that the SCE frequency of smokers who drank green tea was the same as that of non-smokers. Researchers attributed a significant inhibitory effect on smoking-induced SCE by *Camellia sinensis*. "Chemopreventive effect of green tea *Camellia sinensis* among cigarette smokers" Shim, JS et al, Cancer-Epidemiol-Biomarkers-Prev. 1995, Jun; 4 (4): 387-91

CLAIMS

1. A method for extracting a synergistic and it's biological activity maintaining compound from raw material (leaves) *Camellia sinensis*, where the used extraction medium is water and the extraction takes place in a container which is non-reactive with the raw material, being preferably non-metallic container, said method comprising the steps:

- the amount of *Camellia sinensis* is elected between 20 - 70 gm per liter of water for producing biological active extract with approximately 20 - 90% polyphenols,
- *Camellia sinensis* and water is heated in the extraction process at a temperature below boiling point of water but over 60° C at least one heating period at said temperature.

2. A method according to claim 1 wherein the used extraction period is between 20 - 40 minutes.

3. A method according to claim 1 wherein multiple extraction is used by drawing off water medium and adding water to the raw material.

4. A synergistic and it's biological activity maintaining compound extracted from *Camellia sinensis* by using water as extraction medium having produced according to the method claimed in claim 1 **characterized** in that said compound comprises 20 - 90 % polyphenols wherein said polyphenols further comprise EGCG between 10 - 90 %.

5. A compound according to claim 4 **characterized** in that compound is a form of liquid, powder or chrystal.

6. An use of an extracted compound according to claim 4 **characterized** in that said compound is used as food preservative wherein the compound concentration is between 10 mg - 1g per kilo food the amount depending on concentration of

polyphenols in the extract and on the type of food.

7. An use of an extracted compound according to claim 4 **characterized** in that said compound is used in pharmaceutical industry for lowering high serum LDL cholesterol levels of humans when preferred amount of *Camellia sinensis* extract per day per person is between 600 mg - 2.400 mg depending upon concentration of polyphenols in the extracted compound.

8. An use of an extracted compound according to claim 4 **characterized** in that said compound is used in pharmaceutical and dental consumer products industry for eliminating dental caries.

9. An use of an extracted compound according to claim 4 **characterized** in that said compound is used in food processing industry as a food ingredient for protecting against cancer of cigarette smokers.

AMENDED CLAIMS

[received by the International Bureau on 15 December 1998 (15.12.1998);
original claims 1, 4 and 5-9 amended; remaining claims
unchanged (2 pages)]

1. A method for extracting a synergistic and its biological activity maintaining compound from raw material (green leaves) *Camellia sinensis*, where the used extraction medium is water and the extraction takes place in a container which is non-reactive with the raw material, said method comprising the steps:
 - the amount of *Camellia sinensis* is elected between 40 - 50 gm per liter of water for producing biologically active extract with approximately 40 - 50% polyphenols,
 - *Camellia sinensis* and water is heated in a non-metallic container in the extraction process at a temperature below boiling point of water between 90° - 95°C at least one heating period at said temperature,
 - the resulting liquid extract is then dried into a powder by heating resulting in evaporization.
2. A method according to claim 1 wherein the used extraction period is between 20 - 40 minutes.
3. A method according to claim 1 wherein multiple extraction is used by drawing off water medium and adding water to the raw material.
4. A synergistic and its biological activity maintaining single compound extracted from *Camellia sinensis* by using water as extraction medium having produced according to the method claimed in claim 1 **characterized** in that said compound comprises 40 - 50 % polyphenols wherein said polyphenols further comprise EGCG between 30 - 60 %.
5. A single compound according to claim 4 **characterized** in that compound is a form of liquid, powder or crystal.
6. An use of an extracted single compound according to claim 4 **characterized** in that said compound is used as food preservative wherein the compound concentration

is between 10 mg - 1g per kilo food (=0,001 - 0,1 %) preferably 0,01 - 0,05 % , the amount depending on concentration of polyphenols in the extract and on the type of food.

7. An use of an extracted single compound according to claim 4 **characterized** in that said compound is used in food processing industry for lowering high serum LDL cholesterol levels of humans when preferred amount of *Camellia sinensis* extract per day per person is between 600 mg - 2.400 mg depending upon concentration of polyphenols in the extracted compound.

8. An use of an extracted single compound according to claim 4 **characterized** in that said compound is used in food processing industry or in pharmaceutical and dental consumer products industry for eliminating or reducing dental caries.

9. An use of an extracted single compound according to claim 4 **characterized** in that said compound is used in food processing industry as a food ingredient for protecting against cancer of cigarette smokers and to lower high blood pressure.

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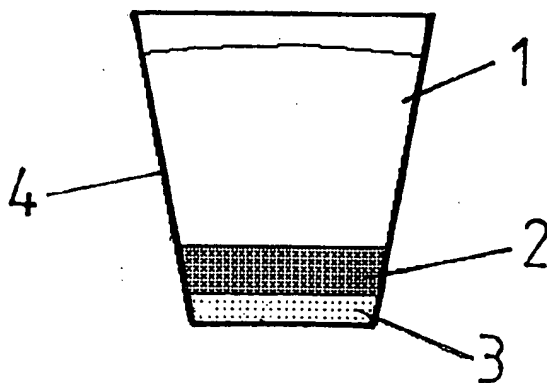


Fig.1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/00412

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 35/78

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, A23F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 742012 A2 (KUREHA CHEMICAL INDUSTRY CO., LTD.), 13 November 1996 (13.11.96), see page 6, line 24 -line 25 and line 37 - line 49 --	1-9
X	GB 1181079 A (VSESOJUZNY NAUCHNO-ISSLEDOVATELSKY INSTITUT CHAINOI PROMYSHLENNOSTI), 11 February 1970 (11.02.70), see page 1, line 43 - line 51, claim 1 and claim 6 --	1-5
X	Patent Abstracts of Japan, & JP,A,4075660, (DAICEL CHEM IND LTD) 10 March 1992 --	1-5

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

12 October 1998

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/00412

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Patent Abstracts of Japan, & JP,A,9104633, (SAN FIELD:KK ET AL) 22 April 1997 --	1-9
A	US 4673530 A (YUKIHIKO HARA), 16 June 1987 (16.06.87) --	6
A	WO 9628178 A1 (INDENA S.P.A.), 19 Sept 1996 (19.09.96) --	7,9
A	File WPI, Derwent accession no. 89-147372, TAIYO CHEM IND CO LTD: "Compsns. acting on dental caries and periodontosis - contain polyphenol cpds. pref. obtd. from tea by extrn. with water"; & JP,A,1090124, 890406 DW8920; JP,B2,6062408B, 940817 DW9431 -- -----	8

INTERNATIONAL SEARCH REPORT
Information on patent family members

27/07/98

International application No.
PCT/FI 98/00412

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
EP	742012	A2	13/11/96	NONE	
GB	1181079	A	11/02/70	NONE	
US	4673530	A	16/06/87	JP 1044234 B JP 1561043 C JP 59219384 A	26/09/89 31/05/90 10/12/84
WO	9628178	A1	19/09/96	AU 5004096 A CA 2215210 A EP 0814823 A IT 1275905 B IT MI950493 A NO 974188 A	02/10/96 19/09/96 07/01/98 24/10/97 16/09/96 11/09/97